art. The salts are referring to salts of hyaluronic acid. These salts do not require undue experimentation. Furthermore, in respect of 35 U.S.C. §112, second paragraph, Applicant has removed the terminologies including "and/or", "(including scar tissue)", "selected from" in the Markush form, thus overcoming the rejection under 35 U.S.C. §112, second paragraph. Applicants have rewritten said claims in accordance with proper domestic terminology. The preamble of claims 218 and 264 now correspond to the preamble of claims 216 and 263, respectively. Therefore, reconsideration of the claims is respectfully requested.

In respect of 35 U.S.C. §112, first paragraph, Applicants have removed the terms "homologues, analogues, derivatives, complexes, esters, fragments and sub-units of hyaluronic acid", and have limited the molecular weight of the form of hyaluronic acid to the range of 150,000 to 750,000 daltons, overcoming the 35 U.S.C. §112, first paragraph rejection. Thus reconsideration of the claim is respectfully requested.

In respect of the Examiner's statement that the term "prevention" lacks enablement (claims 261-264), in that it encompasses protection for days, months, years..., Applicants respectfully submit the following:

In Applicants respectful submission, a person skilled in the art would understand what was meant by the words "prevention" having regard to the teachings of the specification as filed. The application discusses the prevention of topical infection for example see page 35, lines 19-20 and page 67, lines 15-28. The administration of a dosage amount of a form of Hyaluronic Acid and an antimetabolite will prevent or minimize infection. In Applicants' respectful submission, that is what is taught in the Application. In view thereof, Applicants submit that the Application complies with 35 USC 112. However, to more particularly point out in the claims, the teachings in the specification,

Applicants have amended Claims 261-264 to more particularly describe the prevention that is taking place according to Applicants' methods.

To assist the Examiner further with respect to 35 U.S.C. §112, Applicants respectfully draw the Examiner's attention to the following statements:

> Absent any statement of human utility, proof of operativeness in standard test animals is usually adequate for patent purposes; see In Re Bergel et al. (CCPA 1961) 130 USPQ 206; Ex parte Melvin et al. (POBA 1962) 155 USPQ 47.

> Statistically significant tests with standard experimental animals which establish that a chemical compound exhibits the useful pharmaceutical property alleged (in this case treatment and prevention of topical infection) are sufficient to prove the existence of statutory utility; see In Re Krimmel (CCPA 1961) 130 USPQ 215.

Additionally, Applicants submit that the first paragraph of 35 USC 112 requires nothing more than objective enablement. Whether this is achieved by the use of illustrative examples or by broad terminology is of no importance. In re Marzocchi et al. (CCPA 1971) 439 F2d 220, 169 USPQ 367. An assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. In re Dinh-Nguyen et al., (CCPA 1974) 492 F2d 856, 181 USPQ 46; In re Bowen, (CCPA 1974) 492 F2D 859M 181 USPQ 48; In re Armbruster (CCPA 1975) 512 F2d 676, 185 USPQ 152.

A disclosure which contains representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a Claim will possess the alleged utility is all that is required, when

there is no reason to suspect the assertions are not accurate. In re Barr et al. (CCPA 1971) 444 F2d 558, 170 USPQ 330. (This is the case here.)

Nothing is gained by repetitive examples which each assert the same kind of biological activity for every compound embraced by the Claim. In re Surrey (CCPA 1966) 370 F2d 349, 151 USPQ 724. An applicant need not provide a specific example of everything embraced by a broad Claim. In re Anderson (CCPA 1973) 471 F2d 1237, 176 USPQ 331. Each Claim need not be supported by a specific example. Ex parte Morey (POBA 1944) 66 USPQ 191.

Although at one time the Patent Office required at least one "working" example as part of the disclosure of the specification, there is no absolute statutory requirement for such an example if the disclosure is such that one skilled in the art can practise the claimed invention. In re Bordowski et al. (CCPA 1970) 422 F2d 904, 164 USPQ 642; Ex parte Nardi et al. (BPAI 1986) 229 USPQ 79. Use of "prophetic" examples does not automatically make a patent non-enabling merely because there can be no guarantee that the examples would actually work. Atlas Powder Co. v. E.I. DuPont de Nemours & Co. (CAFC 1984) 750 F2d 1569, 224 USPQ 409.

Although a specification preferably should contain a "working" example to ensure that the "how to make and use" and "best mode" requirements of 35 USC 112 are met, a working example is not mandatory if none actually exists and the invention is otherwise disclosed so that one skilled in the art can practice it without undue experimentation. In re Borkowski et al. (CCPA 1970) 422 F2d 904, 164 USPQ 642; In re Gay (CCPA 1962) 309 F2d 769, 135 USPQ 311; In re Stephens et al. (CCPA 1976) 529 F2d 1343, 188 USPQ 649; Ex parte Krenzer (POBA 1978) 199 USPQ 227. Since 35 USC 112 does not demand a "working example", an application cannot be fatally defective merely because it lacks one. In re Long

(CCPA 1966) 368 F2d 892, 151 USPQ 640; In re Honn et al. (CCPA 1966) 364 F2d 454, 150 USPQ 652. In re Bartholome et al. (CCPA 1967) 386 F2d 1019, 156 USPQ 20; Ex parte Kenaga (POBA 1974) 189 USPQ 62. The Patent and Trademark Office has the burden of showing that the disclosure entails undue experimentation. In re Angstadt (CCPA 1976) 537 F2d 498, 190 USPQ 214.

Applicants' disclosure of their invention is addressed to persons skilled in the art. You, the Examiner, in light of the above submissions have the burden of showing that the disclosure does not teach an invention as useful to persons or how the invention is to be used with persons. You have the burden. Applicants respectfully submit this burden has not been overcome. In this regard, the Application is very clear. Human testing is not required to establish the utility of a claimed compound or composition whose intended use is to include human consumption. Once again, see Carter-Wallace Inc. and Riverton Laboratories Inc., (SDNY 1969) 304 FSupp 357, 164 USPQ 73; In re Langer (CCPA 1974) 503 F2d 1380, 183 USPQ 288. All that need be established is that persons skilled in the art can practise the invention for persons (humans). This is clearly taught in the Application. Exemplary amounts for treating the persons are provided. Tests (albeit animal tests) have been provided.

In view thereof, Applicants respectfully submit that the disclosed utility of all methods disclosed must be accepted as accurate. See In re Gazave (CCPA 1967) 379 F2d 973 154 USPQ 92; In re Bundy, (CCPA 1981) 642 F2d 430, 209 USPQ 48.

CLAIM REJECTIONS UNDER 35 U.S.C. §102(b) OR IN THE ALTERNATIVE §103

The Examiner has relied on one prior art reference, Della Valle (United States Patent No. 4,736,024) in rejecting Applicants' application under 35 U.S.C. §102(b) and 35 USC 103. Applicants respectfully submit that their invention is clearly not anticipated or obvious. In fact, the teachings of the prior art cited by

the Examiner teach in a different direction from Applicants' invention, teach away from Applicants' invention and thus, clearly establishes the patentability of Applicants' invention. Thus, the claims of the invention as amended are clearly patentable.

Applicants have carefully considered the "findings of fact" of the Examiner in arriving at her conclusions under 35 U.S.C. § 112, 35 U.S.C. § 102, and 35 U.S.C. § 103 of what a person skilled in the art would understand from reading the Application and the prior art cited by the Examiner. Applicants' Agent has filed previously, declarations of the foremost authorities of hyaluronic acid in the world today. These "Experts" were given a copy of PCT Application PCT/CA 90/00306 published under International Publication No. WO 91/04058 from which the parent application of this Application entered the National Phase in the U.S. under Application Serial No. 07/675,908, the parent application of this Application Serial No. 08/462,147, together with the prior art cited by the Examiner in the parent case which prior art included Della Valle (4,736,024) and asked what persons skilled in the art would understand from the Application and the prior art. These "Experts", who would know what would be understood by persons skilled in the art reading the Application and the prior art as well as the state of the art at the time of the invention, have expressly disagreed with the conclusions reached by the Examiner with respect to the understanding of a person skilled in the art reading Applicants' Application and their ability to understand and use the invention taught and the teachings of the prior art. In each Expert's opinion, the Application fully describes the invention claimed, enables persons skilled in the art to understand and use the invention and concluded the prior art cited by the Examiner <u>does not</u> anticipate Applicants' invention or render the invention obvious. In fact, each one of the Experts was surprised that the invention of Drs. Falk and Asculai worked. Each Expert

previously thought hyaluronic acid to be inert and, if combined with medicine, would be passive - no different than the prior art cited by the Examiner.

Applicants, therefore, enclose with this Response, the Declarations of:

1. Professor Torvard Laurent
2. Dr. Robert Fraser
3. Professor Ian Constable
4. Dr. Eva Turley
5. Dr. Stefan Gustafson
6. Dr. Adrian Moore

who are, Applicants respectfully submit and the Examiner will conclude upon reading their Declarations and Curriculum Vitae, to be Experts with respect to hyaluronic acid and its use. A review of their Curriculum Vitae setting out their qualifications (education, experience, and publications) would leave no doubt. These declarations were filed in the parent case and they apply equally in this case.

Applicants also enclose with this Response, the Declaration of Dr. Sanford Roth (filed in the parent case) who is an Expert in pharmacotherapeutics, especially in the areas of analgesia, inflammation and immunomodulation. The Examiner will note from reading his Curriculum Vitae that his expertise includes NSAIDs (non-steroidal anti-inflammatory drugs). His qualifications are impeccable. He too as an Expert in pharmacotherapeutics (para. 2 of his Declaration) including being an Expert in the use of the chemotherapy of agents used in cancer (see para. 43 of his Declaration) concludes that International Publication No. WO 91/04058 (which corresponds exactly to the parent U.S. Application Serial No. 07/675,908 of this application, United States Application

Serial No. 08/462,147) teaches the invention claimed and enables persons skilled in the art to use the invention. He also offers substantial evidence and insights with respect to the prior art. His conclusions, with respect to anticipation and obviousness, are the same as the other Experts - the invention is inventive and provides unexpected results over the prior art.

Two other Declarations are enclosed.

The first Declaration is by a physician, Dr. George DeVeber, who has extensive experience with hyaluronic acid and, if not an expert, is the equivalent of a person skilled in the art. His conclusions are the same as the Experts.

The other Declaration is that of Stellan Lind. Stellan Lind, while not a technical expert, was involved in the industry relating to hyaluronic acid as a business person and knew the products being experimented with and marketed that contained hyaluronic acid prior to the invention by Drs. Falk and Asculai. He discusses what was known and at what period of time. His Declaration relates to the state of the art and knowledge at the time. In view of his knowledge of the state of the art, when he learned of Drs. Falk and Asculai's invention, Mr. Lind concluded that "Drs. Asculai and Falk had got things absolutely wrong" (see paragraph 9 (a) of his Declaration). To say he "was very surprised is an understatement".

The evidence submitted with this response, in Applicants' respectful submission, is overwhelming - the Expert Evidence establishes that the patent specification adequately describes

(i) the subject matter claimed and enables persons skilled in the art to use the invention, and

(ii) the claimed subject matter, as a whole, is neither anticipated nor obvious in light of the prior art to which the subject matter with respect to which the invention pertains.

Applicants bring the following two recent Court of Appeals decisions to the Examiner's attention.

(a) The first decision is the United States Court of Appeals' decision of *In Re Alton*, 37 U.S.P.Q. 2d, 1578. In that case, the United States Court of Appeals discussed "Sufficiency of Disclosure" under 35 U.S.C. §112 as follows:

> "The issue of whether a patent specification adequately describes the subject matter claimed is a **question of fact**. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). We review questions of fact arising from Board rejections under a clearly erroneous standard. In re Caveney, 761 F.2d 671, 674, 225 USPQ 1, 3 (Fed. Cir. 1985). We review questions of law de novo. Electronic Design & Sales, Inc., v. Electronic Data Systems Corp., 954 F.2d 713, 715, 21 USPQ2d 1388, 1390 (Fed. Cir. 1992).
>
> The adequate written description requirement, which is distinct from the enablement and best mode requirements,[3] serves 'to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material.' In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In order to meet the adequate written description requirement, the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.' In re Gosteli, 872 F.2d 1008,

1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Put another way, 'the applicant must ... convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.' Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Finally, we have stated that '[p]recisely how close the original description must come to comply with the description requirement of section 112 must be determined on a case-by-case basis.' Eiselstein v. Frank, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (quoting Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1116).

"It is well settled that the question of whether a specification provides an adequate written description of the subject matter of the claims is an issue of fact. Therefore, the examiner was in error when he stated that the Wall declaration, which attempted to shed light on whether the '451 specification adequately described the subject matter of claim 70, addressed a legal issue.

Additionally, the examiner interpreted the Wall declaration as offering opinion evidence, rather than factual evidence, on the adequate written description issue. The Wall declaration's assertion that '[m]odifying the residue at position 81 would have no effect on [disulfide bridge formation] because neither [asparagine] nor lysine can participate in disulfide bridge formation' is a factual statement, however. So too is the statement that changing the amino acid at position 81 would involve a modification in subunit IF-2, 'requiring an entirely separate series of manipulations of the complete [amino acid] sequence to generate this different class of analog.' We do not read the declaration as asserting an opinion on the patentability of the claimed IFN- analog. Rather, the declaration is offering factual evidence in an attempt to explain why one of ordinary skill in the art would have understood the specification to describe the modification involving the deletion of the first three amino acids independently of the modification at position 81. Dr. Wall's use of the words "it is my opinion" to preface what someone

of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony.

The examiner (or the Board, if the Board is the first body to raise a particular ground for rejection) 'bears the initial burden ... of presenting a prima facie case of unpatentability.' In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Insofar as the written description requirement is concerned, that burden is discharged by 'presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.' Wertheim, 541 F.2d at 263, 191 USPQ at 97. Thus, the burden placed on the examiner varies, depending upon what the applicant claims. If the applicant claims embodiments of the invention that are completely outside the scope of the specification, then the examiner or Board need only establish this fact to make out a prima facie case. Id. at 263-64, 191 USPQ at 97. If, on the other hand, the specification contains a description of the claimed invention, albeit not in ipsis verbis (in the identical words), then the examiner or Board, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient. Id. at 264, 191 USPQ at 98. Once the examiner or Board carries the burden of making out a prima facie case of unpatentability, 'the burden of coming forward with evidence or argument shifts to the applicant.' Oetiker, 977 F.2d at 1445, 24 USPQ2d at 1444. To overcome a prima facie case, an applicant must show that the invention as claimed is adequately described to one skilled in the art. 'After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument.' Id. at 1445, 24 USPQ2d at 1444.

(b) The second decision is the United States Court of Appeals decision of *In re Michihiko Ochiai, et al.* , 37 U.S.P.Q. 2d, 1127. In that case, the United States Court of Appeals discussed "Obviousness" under 35 U.S.C. § 103 as follows:

> The test of obviousness *vel non* is statutory. It requires that one compare the claim's 'subject matter as a whole' with the prior art 'to which said subject matter pertains.' 35 U.S.C. § 103. **The inquiry is thus highly fact-specific by design**. This is so 'whether the invention be a process for making or a process of using, or some other process.' *Kuehl*, 475 F.2d at 665, 177 USPQ at 255. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

(emphasis added by Applicants' Agent)

As the two issues depend on the facts (whether a patent specification adequately describes the subject matter is a question of fact and the comparison of the "claims' 'subject matter as a whole' with the prior art 'to which said subject matter pertains'...is thus highly fact-specific by design."), the evidence of the Experts and the evidence of the other witnesses must be examined in detail. In Applicants' respectful submission, the evidence is overwhelming. The Examiner will conclude, in Applicants' respectful submission, that the claimed invention in the Application is enabled and not taught by the prior art or obvious in light thereof.

In responding to this Action, Applicants have also amended the claims to more clearly define the invention. It is the dosage amount that is to be administered to the patients, and the methods of use of the dosages, that are both clearly inventive. By administering the dosages claimed, the unexpected benefits of the invention are achieved. The use of the amounts of the form of hyaluronic

acid in the dosages alters the distribution and performance of the medicines/therapeutic agents in the human body and produces an unusual targeting for underperfused tissue and/or pathological tissue (see page 24, lines 13-17 of the Application). Nowhere has this been taught or been expected from the state of the art as evidenced by the Experts' Declarations. These unique dosages and unique methods of treating the patients with these dosages is, according to the Experts, disclosed to persons skilled in the art in the Application so that such persons can use these dosages. The medicines/therapeutic agents in the dosages are those known for specific uses. By using those medicines/therapeutic agents with the form of hyaluronic acid, the form of hyaluronic acid "potentiates the action of the drugs" (see paragraph 4 of Professor Torvard Laurent's Declaration) and "if the said medicines or therapeutic agents are useful for the treatment of said disease or condition, the medicine/therapeutic agent is effectively transported to the site in the body where the treatment is intended to target the medicine or the therapeutic agent, as the case may be, to the site of the disease/condition in need of treatment" (see paragraph 15 of Dr. Fraser's Declaration). The statements of the other Experts are to the same effect. Since the dosages are unique and since the methods of treatment by the use of the dosages are unique and the use of the dosages provide unexpected utility, the claimed dosages and claimed methods are, in Applicants' respectful submission, patentable.

The claims for these dosage amounts and methods of treatment using the dosage amounts have been amended to reflect the described characteristics. The Application supports this amendment both implicitly and explicitly. No new matter has been added.

There is no reason to doubt the effective workings of the teachings of the Application (see for example, paragraphs 41-46 of Dr. Roth's Declaration). In this

regard, the Examiner is directed to the Experts' Declarations. These are the world's leading Experts relating to hyaluronic acid. Hyal Pharmaceutical Corporation has retained most of these Experts as Consultants because of their expertise but, as stated by each of these individuals, acting as a Consultant for Hyal would not deter them from their objectivity in dealing with the invention forming the subject matter of this Application.

With respect to the leading Expert in the world, Professor Torvard Laurent, there is no indication that he is a Consultant and the Examiner will, therefore, conclude has not been retained by Hyal Pharmaceutical Corporation as a Consultant. While Professor Torvard Laurent's Declaration is brief the Declaration is complete with respect to his credentials and his understanding of the teachings of the Application and inventiveness of the subject matter claimed.

35 U.S.C. §102(b) OR IN THE ALTERNATIVE §103/DELLA VALLE 4,376,024 REJECTION

The Examiner asserts Della Valle, U.S. Patent 4,376,024 and states that the said document describes the invention. The Experts are clear about this document and its teachings. U.S. Patent 4,376,024 does not describe the invention. The Examiner is in error in her conclusions of what Della Valle teaches. The said document as addressed to persons skilled in the art does not lead one to the claimed invention. Della Valle does not teach Applicants' dosages or the methods of treatment using the dosages as taught by Applicants' Application. Della Valle, as stated by the Experts, teaches very small dosages (drops) containing less than 0.2 mg of HA per drop applied to the cornea of the eye together with the medicine. As the Experts have stated, these dosages provide a film and a "retard" effect. The Experts state that the film of hyaluronic acid provided takes no active part in delivery of the medicine from the site of administration to the site in need of treatment (as in Applicants' claimed

invention). Della Valle's dosages sit there and stick to the eye (are adhesive to the eye) and provide a film from which the medicine leaches and thus, provides the "retard" effect. When the medicines leach or leak from the formulation, they are absorbed by the eye. This is clear from column 1, line 46 which provides:

> **"When the medicaments are administered in the form of concentrated solutions with elastic-viscous characteristics or in solid form, it is possible to obtain films on the corneal epithelium which are homogenous, stable, perfectly transparent, and which adhere well guaranteeing prolonged bioavailability of the drug, thereby forming excellent preparations with a retard effect."**

This is the area referred to by all of the Experts. Della Valle provides nothing but a film which sticks and the medicine leaches therefrom and is absorbed (see, for example, column 5, lines 3-4).

To Dr. Fraser (and the other Experts), Della Valle teaches depoting of the medicine which leaches out and is absorbed when administered.

See Declarations of:

Professor Torvard Laurent at paragraph 6.
Dr. Robert Fraser at paragraph 49-57.
Professor Ian Constable at paragraph 16.
Dr. Eva Turley at paragraph 18.
Dr. Stefan Gustafson at paragraphs 13-20.
Dr. Adrian Moore at paragraph 13.

Dr. Sanford Roth at paragraph 52, 53.

Dr. Stellan Lind at paragraphs 6-7.

Della Valle does not, in Applicants' respectful submission, teach Applicants' invention. The dosage amounts in Della Valle sit there on the surface (of the eye) from which the medicines leach and are absorbed. There is no recognition of transport or delivery by the dosages of Della Valle from the site of administration into the eye caused by the hyaluronic acid. Della Valle therefore does not describe Applicants' claimed invention and should be rejected as a prior art teaching under 35 U.S.C. § 102.

The claimed dosage amounts are not taught in Della Valle. Neither are the claimed methods of treatment using the dosage amounts claimed.

35 U.S.C. §103 DELLA VALLE (4,376,024) IN COMBINATION WITH DELLA VALLE (5,336,767) AND LOWRY (4,900,550)

With respect to the rejections under 35 U.S.C. § 103, the Examiner will now conclude that firstly, Della Valle does not teach dosages which can facilitate the penetration of the agent through the tissue at the site to be treated through the cell membranes into the individual cells to be treated. These claimed dosages give totally unexpected results (see the Expert Declarations). In fact, the Experts - each one of them was surprised by the invention of Drs. Falk and Asculai. They each thought the invention couldn't work. In this regard, see the Declarations of the Experts as follows:

Professor Torvard Laurent at paragraphs 5 and 6.

Dr. Robert Fraser at paragraphs 7-11.

Professor Ian Constable at paragraph 1(c), 2, 3.

Dr. Eva Turley at paragraphs 2, 3, 4.

Dr. Stefan Gustafson at paragraph 5, 6.

Dr. Adrian Moore at paragraphs 3, 4.

Dr. Sanford Roth at paragraph 6, 8, 59.

Mr. Stellan Lind at paragraphs 6, 9(a), 9(b).

The fact that the dosage amounts and method of treatment using those dosage amounts claimed by Applicants give unexpected utility even to the Experts i.e., dosages which can facilitate the penetration of the agent through the tissue at the site to be treated through the cell membranes into the individual cells to be treated, additionally supports the inventiveness (unexpected utility, totally unexpected to the Experts as well as persons skilled in the art) is further evidence of invention. There is no recognition by anyone before these inventors that the dosage amounts claimed having the characteristics set out would provide delivery from the site of administration to the site in need of treatment. There is nothing in Della Valle to lead anyone, as stated by the Experts, to so conclude. These dosage amounts and the methods of administration of these dosage amounts are, therefore, new, useful, and give unexpected results and thus, are in Applicants' respectful submission patentable.

In light of the above, Della Valle has, in Applicants' respectful submission, been addressed as not teaching the present invention and thus the combination of Della Valle with any or all of Della Valle (5,336,767) and Lowry is not possible since there lacks not only teaching of the invention but motivation to combine the references is also lacking.

The Examiner is respectfully requested to withdraw the grounds for rejecting Applicants' claimed invention on the basis of Della Valle (4,736,024) in combination with Della Valle (5,336,767) and Lowry under 35 U.S.C. § 103.

Furthermore, Applicants have now shown by expert testimony that Della Valle (4,736,024) is irrelevant. Della Valle et al (5,336,767), the Examiner purports to teach the administration of esters of hyaluronic acid with drugs including antibiotics, antibacterials and antiviral agents. Although the enclosed declarations are directed to Della Valle (4,736,024), after careful review of Della Valle (5,336,767), the comments found in the declarations in Applicants' opinion, are applicable to the teachings of Della Valle (5,336,767). Della Valle (5,336,767) does not teach, infer, nor imply a method of treating a condition or disease in a mammal comprising administering an effective dosage amount of a medicinal or a therapeutic agent for treating a condition or disease wherein the medicinal agent is facilitated for penetration of the agent through the tissue by a sufficient dosage amount of a form of hyaluronic acid at a site to be treated. There is no teaching whatsoever of the use of a form of hyaluronic acid which (a) facilitates penetration, (b) has a molecular weight in the range of 150,000 to 750,000 daltons, and (c) provides a dosage greater than 10mg/70kg person. Furthermore, Applicants have removed the term "esters" from the claims. Applicants respectfully submit there is clearly no motivation to arrive at Applicant's invention. Thus Applicants' invention is neither taught nor inferred in Della Valle (5,336,767), alone or combined with any other reference of record. Therefore, reconsideration of the claims as amended is respectfully requested.

Furthermore, the Examiner relies on Lowry stating that the reference discloses a composition containing hyaluronic acid which is effective as a cell penetrant. Applicants respectfully traverse the conclusion of the Examiner with respect to the teachings of Lowry (United States Patent No. 4,900,550). Lowry purports to disclose a cosmetic formulation for use with a skin care cosmetic regime for accelerating the cell renewal cycle of the skin to provide younger looking skin. Each of the cosmetic formulations listed in columns 3 and 4 of

Lowry's patent is formulated of the specific ingredients to achieve the conditioning of a person's skin. Applicants submit that Lowry does not disclose a method of treating a condition or disease in a mammal comprising administering an effective amount of a medicinal or a therapeutic agent for treating a condition or disease wherein the medicinal agent is facilitated for penetration by a sufficient amount of a form of hyaluronic acid to a site in need of treatment. Furthermore, Lowry does not teach the use of a suitable molecular weight of hyaluronic acid which is taught in Applicants' application. The Examiner will agree that Applicants' invention is based on the treatment of disease and conditions (for example, enhancing the prostaglandin synthesis inhibition in order to deblock macrophage activities) by the effective dosage amount of an agent (for example, acetylsalicylic acid), wherein the form of hyaluronic acid acts as a transporting agent.

In summary, Lowry does not teach the use of a form of hyaluronic acid to deliver medicines or therapeutic agents or any agents. There is nothing in Lowry to teach the delivery of anything by hyaluronic acid. Applicants submit that persons skilled in the art would give Lowry minimal effect and would definitely not think of Lowry in respect of the transport or deliver of medicines or agents. There is no motivation to combine Lowry and Della Valle because there is no recognition of transport by the form of hyaluronic acid. There is no leading, by either or both of the references, to the unexpected utility of Applicants' invention - unexpected unobvious results provided by Applicants' dosage and method of treatment with those dosage namely, targeting, delivery, and transport.

In view of the above submissions, Applicants respectfully submit that the claims in the Application are now allowable over the prior art.

The Examiner will appreciate the extent of the effort Applicants have made in bringing sufficient evidence to the Examiner's attention to enable the Examiner to consider the claims further. Applicants' Agent intends to contact the Examiner after the Examiner's receipt of the response together with the Expert Declarations to arrange an appointment to meet with the Examiner to discuss the Application.

If the Examiner, in the interim, has any questions, she is respectfully requested to contact Applicant's Agent, Ivor Hughes at (905) 771-6414 collect at her convenience.

Respectfully submitted,

Ivor M. Hughes
Registration Number 27,759
Hughes, Etigson
Agent for the Applicant

MKS*kdk

Enclosures

1. ✓ Request for a three month extension of time
2. ✓ Copies of the IDS filed with respect to the parent Patent Application 07/675,908
3. ✓ Specification
4. ✓ Declaration of Professor Torvard Laurent
5. ✓ Declaration of Dr. Robert Fraser
6. ✓ Declaration of Professor Ian Constable
7. ✓ Declaration of Dr. Eva Turley
8. ✓ Declaration of Dr. Stefan Gustafson
9. ✓ Declaration of Dr. Adrian Moore
10. ✓ Declaration of Dr. Sanford Roth
11. ✓ Declaration of Dr. George DeVeber,
12. ✓ Declaration of Stellan Lind